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(54) A DRUG FOR TREATING DIABETIC NEPHROSIS

(57) A medicine for treatment of diabetic nephropathy contains rhein or the salt thereof. It may be supplied in aqueous solution or capsula for oral, such dosage is not larger than 200mg/day. Toxicity of rhein or the salt thereof is low, LD50 is 3.2g/kg. The medicine concentration in blood is still higher in 24 hours after administered rhein by oral. Rhein could effectively control or decrease the hyperglycemia, suppress renal hypertrophy and kidney index in experimental diabetic rats. The urinary albumin execretion was significantly decreased in the diabetic patients treated by rhein.

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Description

TECHNICAL FIELD

[0001] The present invention relates to an anthraquinone carboxylic acid, in particular, to a medicine containing rhein for treatment of diabetic nephropathy.

BACKGROUND OF THE INVENTION

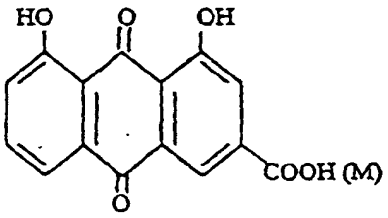
[0002] Diabetes is a frequently occurring disease, and the main medicament for its treatment is insulin at present. However, insulin has no therapeutic effect to the kidney damage caused by diabetes, such as renal hypertrophy, although it can decrease the urinary glucose. Until now, no report has been found on the medicine for treatment of renal hypertrophy caused by diabetes.

DESCRIPTION OF THE INVENTION

[0003] The object of the present invention is to provide a medicine of low toxicity for treatment of diabetic nephropathy.

[0004] The technical solution of the present invention is to prepare an oral medicine for treatment of diabetic nephropathy from rhein or the salt thereof.

[0005] Rhein is a particular medicine in China, that is one of the most common used Chinese medicines. The general formula of rhein can be shown as the following:



[0006] Rhein is one of the chemical components in rhubarb (*Rheum Officinale*, a Chinese herb) and of low toxicity as a natural product. The half lethal dose (LD_{50}) is 3.2g/Kg for SD rats.

[0007] There are not marked gastro-intestinal reactions caused by the oral route of rhein in volunteers treated by rhein. Of the thirty-six volunteers given rhein at dose of 200mg/day (100mg, b.i.d) for 3 days, only 5 persons experience gastro-intestinal disorders. Diarrhea occurred twice or thrice a day in three of these persons, and four times in only one person.

[0008] In pharmacokinetical study, rhein can be easily absorbed from gastro-intestinal trace after the agent is given orally, and the blood concentration of rhein maintains for a longer period. The blood level of rhein reaches peak in one and half hours to three hours after one single dose of rhein at 200mg in health man, and the blood level of them still kept at 200 to 500 ng/ml at 24th hour in volunteers.

[0009] Thus, rhein possesses advantageous as medicine.

[0010] As shown in further investigation of rhein, hyperglycemia in experimental diabetic rats can be controlled or reduced effectively by rhein or sodium rheinate given orally. Particularly rhein is able to control or suppress renal hypertrophy, and decrease the kidney index obviously in diabetic rats. Rhein also can ameliorate the urinary albumin excretion significantly in diabetic nephropathy patients.

[0011] The medicine containing rhein or the salt thereof for treatment of diabetic nephropathy may be supplied in oral capsula or aqueous solution.

[0012] A dosage of rhein up to 200 mg/day is feasible, and may be given twice or thrice a day.

[0013] The following Examples will illustrate the present invention in more details.

EXAMPLE 1

Suppression of renal hypertrophy by rhein in experiment diabetic rats

[0014] Drug: Rhein, a needle-like yellow crystal with melting point of 318-320°C, was prepared into aqueous solution

for oral.

[0015] Diabetic animal model of rat: Adult female SD rats with body weights of 200 to 250 grams were used. Rats were made diabetic by an intra-abdominal injection of Streptozotocin in a dose of 25 mg/Kg/day for 5 days. Only rats with blood glucose level within the range of 13 to 25 mmol/L were recognized as the establishment of the diabetic model.

[0016] The observation was focused on the changes of kidney weight and volume in diabetic rats treated by rhein.

[0017] The experiment was designed as the following:

	Normal rats		Diabetic rats	
	Control	Rhein-treated	Control	Rhein-treated
No. of animals	8		7	6
Dosage of Rhein: mg/Kg/day	0	2	0	2
Distilled water: ml/Kg/day	5	5	5	5

[0018] The experimental results are listed in the following tables.

1. Effect of rhein on the changes of the blood glucose levels (mmol/L)

[0019]

	Normal rats		Diabetic rats	
	Control	Rhein-treated	Control	Rhein-treated
Pre-diabetic	6.62±0.84	6.12±0.34	5.62±1.84	6.23±0.44
After diabetic(weeks)				
1	6.00±0.44	5.92±0.54	19.82±2.84	20.32±1.89
4	6.31±0.36	5.66±0.84	21.12±2.19	19.77±3.87
8	5.82±0.39	6.07±0.49	19.92±3.23	21.00±3.26
12	6.02±0.51	6.22±0.74	20.62±0.64	19.32±1.72

2. Effect of rhein on the kidney weight at the 12th week

[0020]

	Normal rats		Diabetic rats	
	Control	Rhein-treated	Control	Rhein-treated
Kidney Weight (grams)	0.84±0.09	0.72±0.11	1.31±0.73	0.93±0.13
Kidney Volume (ml)	0.794±0.019	0.804±0.210	1.083±0.049	0.834±0.109
Kidney Index ($\times 10^{-3}$)	3.33±0.21	4.04±0.39	7.21±1.30	4.76±0.76

EXAMPLE 2

Suppression of renal hypertrophy by sodium rheinate in experiment diabetic rats

[0021] Drag: aqueous solution of sodium rheinate for oral

[0022] Diabetic animal model of rat: Adult female SD rats with body weights of 200 to 250 grams were used. Rats were made diabetic by an intra-abdominal injection of Streptozotocin in a dose of 25 mg/Kg/day for 5 days. Only rats with blood glucose level in the range of 13 to 25 mmol/L were recognized as the establishment of the diabetic mode.

[0023] The observation was focused on the changes of kidney weight and volume in diabetic rats treated by rhein.

[0024] The experiment was designed as the following:

	Normal rats		Diabetic rats	
	Control	Rhein-treated	Control	Rhein-treated
No. of animals	6	5	6	6
Dosage of Rhein-Na, mg/Kg/day	0	1	0	1
Distilled water, ml/Kg/day	5	5	5	5

[0025] The experimental results are listed in the following tables.

1. Effect of sodium rheinate on the changes of the blood glucose levels (mmol/L)

[0026]

	Normal rats		Diabetic rats	
	Control	Rhein-treated	Control	Rhein-treated
Pre-diabetic	5.33±0.54	6.06±0.72	6.12±0.84	6.17±1.01
After diabetic (weeks)				
1	6.22±0.74	6.52±0.74	22.16±3.64	21.82±2.69
4	5.88±0.66	6.48±0.77	21.57±3.99	19.97±4.17

2. Effect of sodium Rheinate on the kidney weight (g) at the 12th week

[0027]

	Normal rats		Diabetic rats	
	Control	Rhein-treated	Control	Rhein-treated
Kidney Weight (grams)	0.66±0.11	0.59±0.09	0.89±0.22	0.71±0.20
Kidney Index ($\times 10^{-3}$)	4.13±0.09	4.34±0.37	7.94±1.73	5.68±1.16

EXAMPLE 3

Clinical trial of rhein on diabetic nephropathy

[0028] Patients: Twenty-five diabetic patients diagnosed according to the standard of WHO were enrolled in this study.

The fast blood glucose levels were above 250mg/100ml in these patients. Diabetic nephropathy was confirmed morphologically by renal biopsy, or with measurement of urinary protein or albumin excretion in each patient.

[0029] Design: A yellow powder supplied in capsula containing 25mg rhein. The dosage of 100 mg per day (50mg twice a day) rhein was given orally as therapy. All patients were followed at regular intervals for measurement of serum creatinine values and urinary protein or albumin excretion at least for 3 months.

[0030] The experimental results are listed as the following:

1. General clinical data

[0031] All patients enrolled into this study tolerated rhein treatment. None of the recipients receiving rhein at dose of 100 mg per day had gastro-intestinal reactions as vomiting, diarrhea et al.

[0032] There are no liver function abnormally and deterioration of renal function in patients treated with rhein. Blood routine test is normal.

2. Changes of urinary protein excretion

[0033] Of twenty-five diabetic patients given rhein treatment, 18 patients (72%) had obvious decrement of urinary albumin excretion during the 3 months therapy. There are seven diabetic patients (28%) with no change or increase of urinary albumin excretion. The datum are shown in the following table:

Change of urinary albumin Excretion	Treatment after 3 months (No.)
No change	7
Decrease of 25%	4
Decrease of 50%	9
Decrease of 75%	4

[0034] By clinical trial, rhein can decrease the urinary protein excretion in diabetic patients treated by rhein. It is suggested that the medicine possesses therapeutic effect on the kidney damage in diabetic nephropathy, and can be used in clinical practice of diabetes.

INDUSTRIAL APPLICATION

[0035] The medicine provide by the present invention can be absorbed easily from gastrointestinal trace, decrease the urinary protein excretion in diabetic patients treated, obviously reduce kidney index. It can be prepared into oral capsula or oral aqueous solution for the clinical treatment of diabetic nephropathy.

Claims

1. A medicine for treatment of diabetic nephropathy, wherein comprising rhein or the salt thereof.
2. A medicine for treatment of diabetic nephropathy in accordance with claim 1, wherein the said rhein salt is sodium rheinate or potassium rheinate.
3. A medicine for treatment of diabetic nephropathy in accordance with claim 1, wherein it is supplied in capsule or solution for oral.
4. A medicine for the treatment of diabetic nephropathy in accordance with claim 1, wherein the daily dosage of rhein or the salt thereof is not larger than 200mg/day when given orally.

INTERNATIONAL SEARCH REPORT

International application No. PCT/CN98/00175

A. CLASSIFICATION OF SUBJECT MATTER

IPC (6): A61K 31/185

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched(classification system followed by classification symbols)

IPC (6): A61K 31

Documentation searched other than minimum documentation to the extent that such documents are included in the field searched

Chinese Patent Documentation

Electronic data base consulted during the international search(name of data base and, where practicable, search terms used)

WPI(Derwent), CNPAT(CN), JOPAL(JP),Medline,EMBAS,Chemical Abstract.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

	Citation of document, with indication, where appropriate, of the relevant passages	Relevant claim No.
X	JP 平 2 — 149515 （株式会社ツムラ） 08.June,1990(08.06.90),Entire	1-4
X	Eur.J.Drug Metab.Pharmacokinet,Volum19 , No.1 , Jan-Mar1994 , Debord P.et.al , " Influence of renal function on the pharmacokinetics of diacerein after a single oral dose " page13 — 19 ; or Fundam Clin.Pharmacol.,volum7 , No.8 , 1993 , page435 — 441	1-4
X	NATIONAL MEDICAL JOURNAL OF CHINA , volum73 , No.6 , 1993 , Zheng F.,et. al., " effect of Rheum officinal on the proliferation of renal tubular cells in vitro " , page343 — 345	1-4
X	Chinese Medical Journal,volum109 , No.1,1996,Li Leishi, " RHEUM OFFICINALE : A NEW LEAD IN PREVENTING PROGRESSION OF CHRONIC RENAL FAILURE " , page35 — 37	1-4

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 1998 (20.10.98)	05 NOV 1998 (05.11.98)
Name and mailing address of the ISA/ The Chinese Patent Office, 6, Xitucheng Road, Haidian District, Beijing, 100088, China Facsimile No. 86-10-62019451	Authorized officer ZHAO Xiyuan Telephone No. 01062093891

Form PCT/ISA/210(second sheet)(July 1992)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN98/00175

Patent document cited in search report	Publication date	Patent family members	Publication date
JP 平 2-149515	08.06.90	none	

Form PCT/ISA/210(patent family annex)(July 1992)